Symptomatic Intracerebral Hemorrhage following Thrombolytic Therapy for Acute Ischemic Stroke: A Review of the Risk Factors

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Abstract

**Background:** Symptomatic intracerebral hemorrhage (SICH) following thrombolytic therapy for acute ischemic stroke is associated with a high rate of morbidity and mortality. Knowledge of the risk factors associated with SICH following thrombolytic therapy may provide insight into the pathophysiological mechanisms underlying the development of SICH, lead to the development of treatments that reduce the risk of SICH and have implications for the design of future stroke trials. **Methods:** Relevant studies were identified through a search in Pubmed. Included studies used multivariate analyses to identify independent risk factors for SICH following thrombolytic therapy. For each variable that was found to have a significant association with SICH, a secondary literature search was conducted to identify additional reports on the specific relationship between that variable and SICH. **Summary of Review:** Twelve studies met inclusion criteria for the systematic review. Extent of hypodense brain parenchyma on pretreatment CT and elevated serum glucose or history of diabetes were independent risk factors for thrombolysis-associated SICH in six of the twelve studies. Symptom severity was an independent risk factor in three of the studies and advanced age, increased time to treatment, high systolic blood pressure, low platelets, history of congestive heart failure and low plasminogen activator inhibitor levels were found to be independent risk factors for SICH in a single study. Although these data should not alter the current guidelines for the use of rt-PA in acute stroke, they may help develop future strategies aimed at reducing the rate of thrombolysis-associated SICH.

Key Words

Ischemic stroke · Hemorrhagic transformation · Plasminogen activator · Intracerebral hemorrhage · Thrombolytic therapy

Introduction

Thrombolytic therapy is the only available medical treatment for acute ischemic stroke that has been proven to be effective. Intravenously administered recombinant tissue plasminogen activator (rt-PA) has been shown to improve the long-term functional outcome [1, 2] and is recommended for the treatment of eligible acute stroke patients [3–5]. However, the use of thrombolytic therapy is associated with an increased risk of symptomatic intracerebral hemorrhage (SICH).

The risk of SICH in stroke patients treated with rt-PA is approximately 6%. In a recent pooled analysis of 6 randomized trials of intravenous rt-PA for stroke the rate of substantial intracerebral hemorrhage was 5.9%.
in patients treated with rt-PA compared with 1.1% in placebo patients [6]. A meta-analysis of safety data from 15 open-label studies of intravenous rt-PA including 2,639 ischemic stroke patients reported an SICH rate of 5.2% [7]. SICH following thrombolytic therapy is associated with very poor clinical outcomes. The fatality rate is between 50 and 80% and the rate of severe morbidity or mortality exceeds 90% [6, 8–10]. What proportion of poor outcomes is attributable to SICH is, however, not known because there is overlap between risk factors for thrombolysis-associated SICH and risk factors for poor outcome following thrombolytic therapy in the absence of SICH.

Many studies have reported on clinical, radiological and laboratory variables that are associated with an increased risk of SICH following thrombolytic therapy, but rigorous systematic reviews of these studies are sparse. The aim of this report is to summarize this extensive body of literature and to provide a comprehensive overview of the variables that are likely to be independent predictors of SICH following thrombolytic therapy. It is important to note that this systematic review does not address the efficacy of rt-PA treatment in stroke patients at increased risk for thrombolysis-associated SICH and that these patients may still benefit from treatment. A better understanding of thrombolysis-associated risk factors may, however, provide insight into the pathophysiology of intracerebral hemorrhage following administration of thrombolytics, lead to the development of treatment strategies aimed at reducing SICH risk and help design future clinical trials.

**Methods**

Potentially relevant studies were identified by conducting a Medline/Pubmed search on August 1, 2006, using the following key words: ‘intracerebral’, ‘hemorrhage’, ‘stroke’ and ‘thrombolytic’. The query was limited to human studies published in the English literature. The reference list of all relevant articles and the authors’ personal libraries were reviewed to identify additional studies. Only studies that used multivariate analysis to identify independent risk factors of SICH associated with thrombolytic therapy for stroke were included. Inclusion of each study was determined by consensus among all authors. We accepted the definitions of SICH used by the authors in each study, although these definitions varied among studies (table 1). Variables that were independently associated with an increased risk of SICH following thrombolysis were abstracted from the literature. For each variable that was found to have a significant association with SICH in 1 of the multivariate analyses, a secondary broader literature search was conducted to identify additional articles addressing the relationship between that variable and the occurrence of thrombolysis-associated SICH. A broader literature review is also presented for 2 select variable categories (antiplatelet use and MRI characteristics) that have received considerable attention in the scientific literature but that have not been shown to have an independent association with SICH in multivariate analyses.

**Summary of Review**

The Pubmed query identified 635 articles, of which 11 were included in this systematic review. One additional article that met inclusion criteria was identified through review of reference lists and the authors’ libraries [9]. Therefore, the prespecified search strategy resulted in 12 articles that met the inclusion criteria for this systematic review [8–19]. Table 1 provides an overview of these studies. Table 2 lists the independent risk factors for SICH identified by these studies.

**CT Characteristics**

Early ischemic changes (EICs) were independently associated with an increased risk of SICH in 6 of the 12 studies [8, 10, 12–14, 16]. Consequently, there is strong evidence to support an association between the presence of EICs on CT and thrombolysis-associated SICH. EICs on CT include hypodensification (hypodensity) of brain parenchyma, hypodensity of cortex (loss of grey-white differentiation) and swelling of the cerebral parenchyma (effacement of sulci and/or compression of ventricle) [20].

When the definition of EICs is considered, it appears that the extent of EICs, particularly the volume of hypodense brain tissue, is an important factor in determining the risk of SICH. Several studies quantified the degree of early infarct signs according to various scales [9–11, 13–18]. For example, the Alberta Stroke Programme Early CT Score (ASPECTS) [13] quantifies EICs. Two studies have shown that in patients treated with intravenous rt-PA, lower ASPECTS scores are associated with an increased risk of SICH [13, 21]. Similarly, studies that have quantified the degree of CT changes as involving less or more than 33% of the middle cerebral artery (MCA) territory have found higher SICH rates in patients with more extensive early infarct signs [10, 16]. Specifically, Tanne et al. [10] reported a 3-fold increased risk of SICH in patients with early infarct signs involving ≤½ of the MCA territory and a 6-fold increased risk when involving >½ of the MCA territory compared to patients without early infarct signs. Further evidence stressing the importance of quantifying the extent of early infarct signs stems from the results of the European Cooperative Acute Stroke Study (ECASS I) [22]. In this study an increase in fatal intracerebral hemorrhages was found with increasing extent of early infarct signs in patients treated with rt-PA [23]. A possible limitation of the use of EICs as a predictor of SICH risk is the lack of agreement among physicians in categorizing early CT changes [13, 23–28]. A second limitation is that all reported studies are based on CT scans which were obtained several years ago. Because CT technology improves continuously, the results of these studies may not be entirely applicable to scans obtained with today’s state-of-the-art CT technology.

**Serum Glucose Levels or History of Diabetes Mellitus**

A history of diabetes, baseline serum glucose or both variables were assessed in each of the 12 included studies and were independently associated with an increased risk of SICH in 6 [9–13, 15]. In univariate analysis baseline serum glucose showed a significant association with SICH in 6 of 8 studies for which
### Table 1. Overview of studies

<table>
<thead>
<tr>
<th>Authors and year</th>
<th>Study</th>
<th>Cohort and treatment window</th>
<th>SICH Rate %</th>
<th>SICH definition</th>
<th>Independent risk factors of SICH</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group investigators [8], 1997</td>
<td>NINDS rt-PA stroke trial</td>
<td>311 IV rt-PA 312 controls &lt;3 h</td>
<td>6.4 0.6</td>
<td>neurological deterioration temporally related to ICH</td>
<td>1. NIHSSS (5 categories) 1.2 CT edema or mass effect</td>
<td>1.8 (1.2–2.8) 7.8 (2.2–27.1)</td>
</tr>
<tr>
<td>Demchuk et al. [11], 1999</td>
<td>5-center cohort study</td>
<td>138 IV rt-PA &lt;3 h</td>
<td>9</td>
<td>neurological deterioration temporally related to ICH</td>
<td>1. serum glucose (per 5.5 mmol/l) or diabetes mellitus*</td>
<td>2.26 (1.05–4.83)</td>
</tr>
<tr>
<td>Jaillard et al. [12], 1999</td>
<td>MAST-E</td>
<td>156 SK 154 control &lt;6 h</td>
<td>21 2.6</td>
<td>neurological deterioration temporally related to HT</td>
<td>1. CT hypodensity (present or absent) 2. history of diabetes mellitus 3. decreased level of consciousness</td>
<td>3.1 (1.3–7.4) 3.7 (1.3–10.6) 2.7 (1.1–6.4)</td>
</tr>
<tr>
<td>Barber et al. [13], 2000</td>
<td>2-center cohort study</td>
<td>156 IV rt-PA &lt;3 h</td>
<td>6.4</td>
<td>neurological deterioration temporally related to ICH</td>
<td>1. ASPECTS value (≤7 vs. &gt;7) 2. serum glucose (≤10 vs. &gt;10 mmol/l)</td>
<td>14 (2–117) 4.9 (1–21)</td>
</tr>
<tr>
<td>Dubey et al. [14], 2001</td>
<td>2-center cohort study</td>
<td>70 IV rt-PA &lt;3 h</td>
<td>8.6</td>
<td>≥2-point worsening on NIHSS associated with a parenchymal hematoma</td>
<td>1. CT basal ganglia hypodensity (HF units) 2. NIHSSS</td>
<td>p = 0.0018 p &lt; 0.05</td>
</tr>
<tr>
<td>Kase et al. [15], 2001</td>
<td>PROACT II</td>
<td>110 IA proUK 64 controls &lt;6 h</td>
<td>10.9 1.3</td>
<td>≥4-point worsening on NIHSS associated with ICH</td>
<td>1. serum glucose (per mg/dl)</td>
<td>1.013 (1.003–1.023)</td>
</tr>
<tr>
<td>Larrue et al. [16], 2001</td>
<td>ECASS II</td>
<td>407 IV rt-PA 386 control &lt;6 h</td>
<td>8.9 3.4</td>
<td>≥4-point worsening on NIHSS associated with ICH</td>
<td>1. history of congestive heart failure 2. CT hypodensity (0, ≤33 or &gt;33%) 3. age</td>
<td>3.71 (1.72–8.02) 2.03 (1.18–3.52) 1.04 (1.01–1.08)</td>
</tr>
<tr>
<td>Gilligan et al. [17], 2002</td>
<td>ASK</td>
<td>134 SK 136 control &lt;4 h</td>
<td>21 4</td>
<td>significant neurological deterioration and a parenchymal hemorrhage with mass effect</td>
<td>1. SBP</td>
<td>1.03 (1.01–1.05)</td>
</tr>
<tr>
<td>Tanne et al. [10], 2002</td>
<td>Multicenter rt-PA acute stroke survey</td>
<td>1,205 IV rt-PA &lt;3 h</td>
<td>6</td>
<td>neurological deterioration temporally related to ICH</td>
<td>1. diabetes mellitus 2. platelets (per 50,000 increase) 3. early CT changes &lt;33% of MCA 4. early CT changes &gt;33% of MCA</td>
<td>3.87 (1.73–8.69) 0.71 (0.52–0.97) 3.37 (1.41–8.05) 6.70 (2.14–21.01)</td>
</tr>
<tr>
<td>Ribo et al. [18], 2004</td>
<td>Single-center cohort</td>
<td>77 IV rt-PA &lt;3 h</td>
<td>7.9</td>
<td>≥4-point worsening on NIHSS associated with ICH</td>
<td>1. PAI-1 (&lt;21.4 ng/ml)</td>
<td>12.8 (1.2–139.2)</td>
</tr>
<tr>
<td>Hill et al. [9], 2005</td>
<td>CASES</td>
<td>1,135 IV rt-PA &lt;3 h</td>
<td>4.6</td>
<td>neurological deterioration temporally related to ICH</td>
<td>1. serum glucose (per 5 mmol/l) 2. time onset to treatment (per 30 min)</td>
<td>1.6 (1.2–2.3) 1.2 (1.0–1.5)</td>
</tr>
<tr>
<td>Cocho et al. [19], 2006</td>
<td>3-center cohort study</td>
<td>114 IV rt-PA &lt;3 h</td>
<td>7</td>
<td>≥4-point worsening on NIHSS associated with ICH</td>
<td>1. NIHSSS</td>
<td>1.3 (1.0–1.6)</td>
</tr>
</tbody>
</table>

Figures in parentheses represent 95% confidence intervals. NINDS = National Institute of Neurological Disease and Stroke; IV = intravenous; NIHSSS = National Institutes of Health Stroke Scale score; CT = computed tomography; MAST-E = Multicenter Acute Stroke Trial-Europe; SK = streptokinase; HT = hemorrhagic transformation; ASPECTS = Alberta Stroke Program Early CT Score; HF = Hounsfield; PROACT = Prolyse in Acute Cerebral Thromboembolism; IA = intra-arterial; proUK = prourokinase; ECASS = European Cooperative Acute Stroke Study; ASK = Australian Streptokinase Trial; SBP = systolic blood pressure; MCA = middle cerebral artery; PAI = plasminogen activator inhibitor; CASES = Canadian Alteplase for Stroke Effectiveness Study.

1 NIHSSS categories were <5, 6–10, 11–15, 16–20 and >20.
2 Primary multivariate model did not include history of diabetes mellitus (DM) because of close association between serum glucose level and DM. In a separate multivariate model which included DM instead of glucose level DM was a significant predictor of SICH (odds ratio = 7.46; 95% CI = 2.68–96.4).
3 Both rt-PA-treated patients and controls received fixed dose IV heparin infusion during IA therapy.
4 Seventeen patients received additional IA rt-PA; 146 patients were enrolled in randomized trials of adjuvant neuroprotectives; 137 patients were treated outside 3-hour time window.
the results of this analysis were reported [8–11, 13–15, 19]. In contrast, univariate analysis between history of diabetes and SICH was significant in only 3 [10–12] of 6 studies that reported on this relationship [8, 10–12, 15, 29]. Out of 4 studies that reported the univariate analysis for both serum glucose and history of diabetes, 2 reported significant associations between both risk factors and SICH [10, 11] and 2 only showed a significant association between serum glucose and SICH [8, 15]. These results suggest that elevated serum glucose on admission or a history of diabetes mellitus places a patient at increased risk for SICH following rt-PA.

**Symptom Severity**

In 3 studies greater symptom severity, as assessed by the National Institutes of Health Stroke Scale (NIHSS), was independently associated with SICH [8, 14, 19]. In the Multicenter Acute Stroke Trial-Europe study the interaction between decreased level of consciousness and streptokinase treatment was associated with an increased risk of SICH [12]. As symptom severity correlates with infarct volume [30], the association between symptom severity and SICH is consistent with the notion that SICH is most likely to occur in the setting of extensive and severe cerebral ischemia. The lack of an independent association between symptom severity and SICH in most of the evaluated studies may be explained by masking of this association by other variables. Specifically, NIHSS score is significantly associated with EICs on CT [31].

**Age**

Advancing age was found to be an independent risk factor of SICH in 1 of the included studies [16]. In 3 other studies advancing age was associated with SICH in univariate analysis but did not remain significant after other variables were added to the model [8, 10, 19]. However, in multivariate analyses of risk factors for hemorrhage in the pooled analysis of the NINDS, ECASS and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trials, age was associated with the occurrence of substantial parenchymal hematoma [6]. This discrepancy may be the result of differences between the statistical models used for the pooled analysis and those used for the studies included in this review. For example, the pooled analysis had greater power to detect predictors because of a larger sample size. It also used a different outcome variable (substantial parenchymal hematoma instead of SICH) and evaluated different dependent variables (e.g. early CT infarct changes were not included).

Because most studies excluded patients above age 80, the risk of SICH in this population has not been well studied. However, in the Canadian Alteplase for Stroke Effectiveness Study study, which was included in this review, and 1 additional study which did not meet inclusion criteria for this review, the rate of SICH in rt-PA-treated patients older than 80 years was not different from patients younger than 80 [32, 33]. Moreover, in the NINDS tPA trial, which had no upper age limit in the latter part of the study, no association between age and SICH was found. A recent systematic review that compared stroke outcome after rt-PA in older versus younger patients also found no increased risk of SICH with advancing age [34]. These data suggest that acute stroke patients above 80 should not be excluded from treatment with tPA based on their SICH risk. In contrast, advanced age has been identified as a risk factor for SICH in patients treated with tPA based on their SICH risk. In contrast, advanced age has been identified as a risk factor for SICH in patients treated with intravenous thrombolitics for acute myocardial infarction [35]. This discrepancy may reflect differing pathophysiology of SICH in patients with myocardial infarction compared to stroke patients or may be the result of increased power to detect risk factors in the larger acute myocardial infarction trials.

**Time to Onset of Treatment with Thrombolytic Agent**

Only 1 study identified onset of treatment with thrombolytic agent as an independent risk factor of SICH in multivariate anal-

<table>
<thead>
<tr>
<th>SICH risk factor</th>
<th>Number of studies that evaluated variable</th>
<th>Number of studies that identified variable as independent risk factor in multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT hypodensity</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Elevated serum glucose or history of diabetes mellitus</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Time to treatment</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>High systolic blood pressure</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Low platelets</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Low plasminogen activator inhibitor</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1 History of any cardiac disease was assessed in 8 of the 12 studies included in this systematic review. History of congestive heart failure, specifically, was assessed in 3 of these studies and was an independent risk factor for SICH in 1. Other cardiac conditions were not found to be an independent risk factor of SICH in any of the studies.
yis [9]. In 1 other study there was an association in univariate but not in multivariate analysis [19]. Also in the pooled analysis of the NINDS, ECASS and ATLANTIS trials no independent association between onset of treatment with thrombolytic agent and risk of substantial intracerebral hemorrhage was shown [6]. Most of the studies reviewed here allowed treatment up to 3 h, whereas only few allowed treatment up to 6 h. Therefore, the risk of SICH at later treatment times is not well established.

**Blood Pressure**

Only 1 study included in this review found a significant association between blood pressure and SICH [17]. In this study higher systolic blood pressure was an independent predictor of SICH. In 1 additional study systolic blood pressure was significant in univariate but not in multivariate analysis [10]. The risk of SICH associated with uncontrolled severe hypertension is not known because these patients were excluded from all stroke thrombolysis trials and clinical guidelines recommend that such patients are excluded from rt-PA treatment in routine clinical practice [4, 36]. In the Global Use of Strategies to Open Occluded Coronary Arteries trial, which evaluated the effect of thrombosis for acute myocardial infarction, higher blood pressures were associated with an increased risk of SICH [35].

**Thrombocytopenia**

A very low platelet count (<100,000/μl) is a contraindication for the routine use of rt-PA [3, 36] and thrombolytic trials have generally excluded these patients. Therefore, data are only available on patients with platelet counts exceeding 100,000/μl. Platelet counts were evaluated as a potential independent variable in 4 of the reviewed studies [10, 15, 16, 29], of which only 1 identified lower platelet counts as an independent risk factor for SICH [10]. In the other 3 studies no association was found in either univariate or multivariate analyses [15, 16, 29].

**History of Cardiac Disease**

Different definitions for ‘history of cardiac disease’ were used across studies, but they are grouped here under the same paragraph for clarity. History of cardiac disease was independently associated with an increased risk of SICH in only 1 of the reviewed studies [16]. In this study, prior congestive heart failure increased the risk of hemorrhage [16]. In the Multicenter rt-PA Acute Stroke Survey ‘cardiac disease other than atrial fibrillation’ was associated with an increased risk of SICH when only clinical variables were included in the multivariate model but not after adding imaging and laboratory variables [10]. In this and 1 other study, history of atrial fibrillation was associated with an increased risk of SICH in univariate but not in multivariate analysis [10, 12].

**Antiplatelet Agents**

Concomitant use of antithrombotic agents was prohibited in most thrombolytic stroke studies, but prior treatment with aspirin (ASA) was allowed. ASA use was not found to be an independent predictor of SICH in any of the reviewed studies. Only in 1 study, the Multicenter rt-PA Acute Stroke Survey, was pretreatment with ASA associated with an increased risk of SICH in univariate analysis, but it did not remain a significant predictor in multivariate analysis [10]. In this same study the use of antiplatelet agents other than ASA (primarily ticlopidine) was independently associated with an increased risk of SICH in a model including only clinical variables, but not in a multivariate model that included clinical as well as laboratory and CT variables. In ECASS II both ASA and an rt-PA-by-ASA interaction were associated with an increased risk of any parenchymal hemorrhage but not SICH [16]. Based on this systematic review there is thus no convincing evidence to support an independent association between prior ASA use and thrombolysis-associated SICH. A recent open prospective study of rt-PA treatment also showed no increased risk of symptomatic bleeding in ASA users compared to patients who did not use ASA [37]. Data on the risk of SICH in patients taking newer antiplatelet agents such as clopidogrel are not available. The only study that tested the interaction between thrombolytic and ASA treatment following stroke by random allocation is the Multicenter Acute Stroke Trial-Italy [38]. In this study combination treatment with ASA and streptokinase resulted in an increased death rate compared to streptokinase alone, which was largely attributable to intracranial hemorrhages.

**Biochemical Characteristics**

Endogenous fibrinolysis inhibitors, which are released in the circulation following cerebral ischemia, may interact with rt-PA and modify its effect. For example, plasminogen activator inhibitor (PAI-1) is the main inhibitor of rt-PA and low levels are associated with increased rt-PA activity [39]. Of 2 recent studies that have evaluated this marker, 1 demonstrated an independent association between low levels of PAI-1 and rt-PA-associated SICH [18], whereas another found no such association [19]. A further study has demonstrated higher recanalization rates in patients with low pretreatment levels of PAI-1 [40].

There are several other biochemical variables that may help predict SICH risk following thrombolysis. Thrombin-activated fibrinolysis inhibitor has been associated with an increased risk of SICH in univariate analysis, but this relationship did not remain significant after adjusting for potential confounders [18]. Matrix metalloproteinases (MMPs) are enzymes involved in remodeling of extracellular matrix [41]. MMP-2 and MMP-9 break down components of the basal lamina around cerebral blood vessels. One study demonstrated that increased MMP-9 levels prior to administration of rt-PA increase the risk of parenchymal hemorrhage in univariate analysis [42]. In a rabbit embolic stroke model, administration of an MMP inhibitor decreased the rate of hemorrhagic transformation following thrombolysis with rt-PA [43]. High cellular fibronectin levels, a substance that reflects microvasculature damage, correlate with MMP-9 levels and also have a strong association with hemorrhagic transformation [44].

**MRI Characteristics**

None of the studies that examine baseline magnetic resonance imaging (MRI) characteristics and SICH risk following thrombolytic therapy met inclusion criteria for this review. However, because the use of MRI to predict the response to rt-PA has recently received much attention in the scientific literature, a secondary review of this topic is included. In 1 study volume of ischemic tissue on diffusion-weighted MRI, with an apparent diffusion coefficient \( \leq 1.5 \times 10^{-6} \text{mm}^2/\text{s} \), was the single independent predictor of any ICH [29]. One recent preliminary presentation showed that larger diffusion-weighted MRI lesion volume was the single independent predictor of SICH among several clinical and MRI-based variables [45]. Although these data suggest
MRI parameters may help predict SICH risk, future studies are needed to confirm this observation.

Four other MRI variables have been postulated to predict rt-PA-related SICH. First, the degree of hypoperfusion, specifically low cerebral blood volume on perfusion-weighted imaging, has been identified as a potential predictor of SICH [46]. Second, damage to the blood-brain barrier as evidenced by enhancement on postcontrast T1-weighted images appears predictive of hemorrhage both in animal models [47, 48] and in human studies [49, 50]. Third, delayed gadolinium enhancement of cerebrospinal fluid space on fluid-attenuated inversion recovery images, which has been termed hyperintense acute reperfusion marker (HARM), also reflects disruption of the blood-brain barrier and is associated with an increased risk of hemorrhagic transformation [51]. This variable is, however, not a good baseline marker of SICH risk, as it first becomes apparent on delayed MRI. Last, the presence of microbleeds on pretreatment gradient-echo MRI was hypothesized to be a potential risk factor of SICH based on an observation in a single patient in a small case series [52], but 2 subsequent larger studies found no association between microbleeds and SICH [53, 54].

**Discussion**

This report provides a systematic review of risk factors that have been shown to have an independent association with SICH following thrombolytic therapy for acute stroke. The implications of these data are twofold. First, they provide some insight into the pathophysiological mechanisms underlying the development of SICH. SICH following rt-PA is thought to be the result of reperfusion of cerebral vessels whose integrity has been disrupted by severe ischemia [55, 56]. The increased risk of SICH seen in rt-PA-treated patients with extensive early infarct changes on CT is consistent with this hypothesis, as EICs reflect cerebral edema which develops secondary to ischemic injury of the brain parenchyma, a process that is closely linked to ischemic injury of the cerebral microvasculature. Other indicators of severe cerebral ischemia are large infarct volume with low apparent diffusion coefficient values on MRI and high levels of biomarkers that reflect vascular damage. Although these factors have not yet been studied as extensively as early infarct changes on CT, preliminary data suggest that they too may predict subsequent development of SICH. The damaging effect of ischemia to the blood-brain barrier appears to be aggravated in the presence of hyperglycemia. This was also demonstrated in early animal experiments [57] and suggested a decade ago by Broderick et al. [58], based on observations in 2 human stroke cases. The current review supports this concept by demonstrating that hyperglycemia is a risk factor for thrombolyis-associated SICH. Because of the close association between history of diabetes mellitus and serum glucose on admission it is difficult to determine which of these 2 factors more strongly predicts SICH risk. Our review of univariate analyses suggests greater importance of serum glucose than history of diabetes. Conceptually the 2 factors may contribute to an increased risk of SICH via different pathophysiological mechanisms. Chronic microvascular damage secondary to long-standing diabetes may predispose vessels to rupture in the setting of ischemia, whereas biochemical sequelae of hyperglycemia may contribute to acute injury of the blood-brain barrier [57], leading to increased hemorrhage rates [59]. A final factor in the pathophysiology of SICH may be a milieu that enhances the potency of rt-PA. This is exemplified by the finding that low levels of the endogenous occurring rt-PA inhibitor PAI-1 may be associated with an increased risk of SICH. However, because identification of an independent association does not confirm a causal relationship between a risk factor and SICH, inferences regarding potential pathophysiological mechanisms should be viewed with caution.

Second, knowledge of the key risk factors of thrombolysis-associated SICH may lead the way to future stroke trials aimed at improving the efficacy of thrombolysis by reducing the risk of SICH. One example is to compare the routine rt-PA dosing regimen to a regimen that is adjusted based on knowledge of pretreatment levels of fibrinolytic enzymes (such as PAI-1) that modulate the potency of rt-PA. A randomized trial between standard and aggressive serum glucose control in stroke patients who receive rt-PA is another example. Aggressive glucose control may reduce the SICH rate and may also improve the outcome in patients who do not develop SICH [60]. This is suggested by a post hoc analysis of the NINDS tPA trial, which demonstrated a deleterious effect of hyperglycemia on stroke outcome and a decreased chance for neurological improvement even in the absence of SICH [61]. Similar results have been reported by others [62–64].

Our review has several limitations. First, it does not address the SICH risk posed by the presence of a combination of risk factors in the same individual. Although the effect may simply be cumulative, there is evidence indicating that the interaction between multiple risk factors may be synergistic. According to 1 study, the calculated chance of SICH in patients without infarct signs on CT is 5% with average glucose levels (150 mg/dl) and 13% with high glucose levels (350 mg/dl), whereas the chance of SICH in patients with infarct signs on CT is 26% with av-
erage and 52% with high baseline glucose levels. Second, none of the referenced studies were specifically powered to detect risk factors for thrombolysis-related SICH. This results in a relatively high likelihood of failing to identify a risk factor even though an association exists (high chance of type II error). Type I errors (falsely identifying a variable as a risk factor even though no association exists) may also have been introduced in some of the studies because too many dependent variables were included in the statistical models without correcting for multiple comparisons. Third, in the reviewed studies patients with extreme values of any of the clinical variables were generally excluded (e.g. uncontrolled hypertension, severe hyperglycemia or thrombocytopenia). Our conclusions therefore apply to patients whose clinical parameters fall within the range that is generally felt to be acceptable for intravenous rt-PA treatment according to current guidelines [3, 36]. Fourth, the prespecified inclusion criteria for this review resulted in a fairly homogeneous set of studies, but differences, inherent to any review, are present. These include differences in study size, SICH definition, thrombolytic agent used, route of administration and treatment time window. There may also be factors that are independently associated with an SICH risk but that were not included in the univariate analysis of any of the studies. For example, in the Desmoteplase in Acute Ischemic Stroke trial higher dosing of thrombolytics was associated with unacceptably high rates of SICH (27%), whereas more moderate dosing was not (SICH rate 2.2%), suggesting that dose of thrombolytic is a risk factor for SICH [65].

Different classification schemes for thrombolysis-associated hemorrhage have been used. The most common classification distinguishes symptomatic from asymptomatic hemorraghes. Because of its widespread use and clinical significance the search strategy for this review was based on this classification and included only studies with data on SICH as the outcome variable. This classification may, however, not be optimally suited to determine the pathophysiology of thrombolysis-associated hemorrhage because hemorrhage severity does not correlate strongly with the degree of clinical worsening [66, 67]. A classification based on brain imaging that distinguishes between hemorrhagic infarcts and parenchymal hematomas has been used by the ECASS investigators and may be more useful in this respect [22, 66, 68, 69]. In a recent review, Trouillas and von Kummer [66] conclude that hemorrhagic infarctions, characterized by punctate/petechial lesions within the ischemic infarct, are generally not clinically significant and are not related to thrombolytic therapy, whereas parenchymal hematomas, which are confluent/homogeneous lesions that originate from within the ischemic lesion, are often associated with clinical deterioration and are more common following thrombolytic therapy.

The aim of this study was to provide an up-to-date and comprehensive overview of variables that are likely to be independently associated with risk of SICH following thrombolytic therapy. A systematic review was the most feasible methodology to achieve this aim. Pooled analysis and meta-analysis are alternative methodologies that can be used to study the association between predictor variables and thrombolysis-associated SICH. Although these methodologies provide more quantitative data, several limitations made them inappropriate for achieving the stated aim. These include lack of access to primary data for pooled analysis, inability to evaluate whether risk factors are independently associated with SICH for meta-analysis and lack of data on specific risk factors in many of the studies for both types of analysis. Future studies using meta-analysis to evaluate the association between individual risk factors such as serum glucose and SICH could, however, complement this review.

The data presented in this review should not be used to alter current clinical practice guidelines. On the one hand, rt-PA should not be withheld from patients with ≥1 SICH risk factors, as these patients may still benefit from thrombolytic therapy. This was indirectly addressed in a post hoc analysis of the NINDS t-PA trial data [70]. In this study, despite higher SICH rates, the chance of a favorable outcome was significantly greater in the subgroup of patients with severe symptoms at presentation (NIHSSS >20) and there was a trend towards better outcome in patients with mass effect or edema on baseline CT [70]. On the other hand, variables that are current contraindications for the use of intravenous rt-PA should not be disregarded because they were not identified as independent predictors of SICH in this systematic review. For example, history of recent head trauma is a contraindication for the use of rt-PA [3, 5], but this variable was not evaluated in any of the reviewed studies because patients with significant head trauma were excluded from all thrombolytic stroke trials.

In summary, this systematic review identified extensive early infarct changes on CT, elevated serum glucose or history of diabetes mellitus, symptom severity, older age, low PAI-1 levels, increased time to treatment, high systolic blood pressure, low platelet counts and history of prior congestive heart failure as risk factors for thrombosis.
bolysis-associated SICH. Future research is required to determine whether any therapeutic interventions can reduce the SICH rate and thereby enhance the effectiveness of rt-PA.

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Risk Factors of Thrombolysis-Associated SICH


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